

**REMARKS****Introductory Comments**

Claims 1, 3-6, 10 and 11 were examined in the Office Action under reply and stand variously rejected under (1) 35 U.S.C. §112, first paragraph (claims 5 and 6); and (2) 35 U.S.C. §103(a) (claims 1, 3-6, 10 and 11). These rejections are believed to be overcome for reasons discussed below.

Applicant acknowledges with appreciation the withdrawal of the previous rejections under 35 U.S.C. §112, second paragraph, as well as the rejections under 35 U.S.C. §102, as these rejections were not reiterated.

**Overview of the Amendments**

Claims 5 and 6 have been cancelled. Cancellation of these claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to pursue the subject matter of the cancelled claims in another application.

**Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 5 and 6 were rejected under 35 U.S.C. §112, first paragraph, as “failing to comply with the written description requirement.” Office Action, page 3. The Office asserts there is “no disclosure in the specification as originally filed that the dosages disclosed in page 3 of the specification are used to ‘contact cells’ *in vivo*” and “it is also unclear as to what ‘contacted the cells’ means in the context recited in the claims.” Office Action, page 3. However, applicant respectfully disagrees.

Contrary to the Office’s assertions, there is indeed support for the language of claims 5 and 6 in the specification as filed. In particular, the passage at page 3 regarding concentrations is followed by two paragraphs. The first paragraph (beginning at page 3, line 26) talks about T cell activation *in vitro*. However, the second paragraph (beginning at page 3, line 31) discusses T cell activation *in vivo*. Thus, it is clear that applicant was in possession of the invention as claimed. See, *Vas Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (cited in

MPEP § 2163 and in the Examiner Guidelines on Written Description Requirement). Nevertheless, solely in an effort to advance prosecution, claims 5 and 6 have been cancelled. Accordingly, this basis for rejection no longer applies and withdrawal thereof is respectfully requested.

### Rejections Under 35 U.S.C. §103(a)

The Office rejected claims 1, 3-6, 10 and 11 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,425,940 to Zimmerman et al. (“Zimmerman”) in view of U.S. Patent No. 6,348,191 to Clark et al. (“Clark”). The Office asserts Zimmerman discloses *in vivo* administration of a combination of IL-2 and TNF-alpha for treatment of tumors. The Office correctly notes that Zimmerman fails to describe the use of IL-6 with IL-2 and TNF. Clark is said to disclose that IL-6 can be used in combination with IL-2 for cancer therapy. However, applicant disagrees that this combination renders the present claims obvious.

Section 2142 of the MPEP sets forth the following basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success (for the modification); and (3) the prior art references must teach or suggest all of the claim limitations. Furthermore, the teaching or suggestion and the reasonable expectation of success must both be found in the prior art, not in applicant’s disclosure. The Office has failed to satisfy these criteria. Applicant submits there is no suggestion or motivation to modify either of the references to arrive at the claimed invention.

In particular, in making this rejection, the Examiner states that Zimmerman’s method “results in antigen independent activation of T cells because the method has the same steps as the originally claimed method.” Office Action, pages 3-4, bridging paragraph. However, even if Zimmerman’s method **inherently** produced the result proposed by the Examiner, the Federal Circuit has cautioned inherency does not form a proper basis for a determination of obviousness.

As stated in *In re Newell*, 13 USPQ2d 1248 (Fed. Cir. 1989): “That which is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.” *In re Newell* at 1250, citing *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966).

Moreover, contrary to the Examiner's statements, the cited combination gives neither a suggestion nor an expectation of success for the use of the combination of IL-2, IL-6 and TNF-alpha, as claimed, to activate T cells in the absence of antigen and both must be present in the prior art in order for the Patent Office to make out a *prima facie* case of obviousness. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). It is well known that mixtures of substances can fail to be as effective as individual components due to physical interactions of the individual substances which might result in altered conformation, aggregation or precipitation. Immunological dominance or competition between components is also known to occur. Finally, the FDA requires that the efficacy of new mixtures be shown even if the efficacy of the individual components or other mixtures using the individual components has been demonstrated, further evidencing the unpredictable results obtained with new mixtures. Thus, the teaching of Zimmerman and Clark simply cannot be combined to evidence that the three components, IL-2, IL-6 and TNF-alpha, would be useful for T cell activation as claimed.

As explained in Section 2143.01 of the MPEP, the mere fact that a reference can be modified, does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Without a suggestion to modify either of Zimmerman or Clark evident therein, the only conclusion supported by the record, should the rejection be maintained, is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, “[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): “One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”

Finally, the Office states the synergistic results displayed by applicant's combination are “not germane” to the question of obviousness because the results were obtained using an *in vitro* assay. Office Action, page 4. However, such *in vitro* tests are indeed predictive of *in vivo* activity. Moreover, rigorous correlation between disclosed *in vitro* utility and an *in vivo* activity is not necessary where the disclosure of pharmacological activity is reasonably based upon probative evidence, such as in the present application. *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed.

Cir. 1985). Finally, if applicant's *in vitro* results are not relevant to *in vivo* claims, applicant submits that the results in Clark, cited by the Office, are also not relevant. Clark's only activity assessment is performed *in vitro*. See, Example VI. Moreover, this example only details the use of IL-6 alone and does not even test activity of a combination of IL-6 and IL-2. Finally, Clark, as with Zimmerman, does not expressly suggest using the combination of IL-6 and IL-2 for activating T cells in the absence of antigen.

Based on the foregoing, the rejection of the claims over the combination of Zimmerman with Clark should be withdrawn.

### CONCLUSION

Applicant respectfully submits that the claims define an invention that complies with the requirements of 35 U.S.C. §112 and that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

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